CLAIMS

1. Suspension of microcapsules in an aqueous liquid phase that allows the modified release of at least one active principle (excluding amoxicillin) and is intended for oral administration, characterized in that:

- it comprises a plurality of microcapsules each consisting of a core containing at least one active principle (excluding amoxicillin) and of a film coating that:
  - is applied to the core,
  - controls the modified release of the active principle(s),
  - and has a composition corresponding to one of the following three families A, B and C:
    - ⇨ Family A
      - ◆ 1A - at least one film-forming polymer (P1) insoluble in the tract fluids, present in an amount of 50 to 90 and preferably of 50 to 80% by dry weight, based on the total weight of the coating composition, and consisting of at least one water-insoluble cellulose derivative;
      - ◆ 2A - at least one nitrogen-containing polymer (P2) present in an amount of 2 to 25 and preferably of 5 to 15% by dry weight, based on the total weight of the coating composition, and consisting of at least one polyacrylamide and/or poly-N-vinylamide and/or poly-N-vinyllactam;
      - ◆ 3A - at least one plasticizer present in an amount of 2 to 20 and preferably of 4 to 15% by dry weight, based on the total weight of the coating composition, and consisting of at least one of the following compounds: glycerol esters, phthalates, citrates, sebacates, cetyl alcohol esters and castor oil;
      - ◆ 4A - at least one surfactant and/or lubricant present in an amount of 2 to 20 and preferably of 4 to 15% by dry weight, based on the total weight of the coating composition, and selected from anionic surfactants and/or non-ionic surfactants and/or lubricants, it being possible for said agent to comprise only one or a mixture of the above-mentioned products;
    - ⇨ Family B
      - ~ 1B - at least one hydrophilic polymer carrying groups ionized at neutral pH and preferably selected from cellulose derivatives;
      - ~ 2B - at least one hydrophobic compound different from A;
    - ⇨ Family C
      - ◆ 1C - at least one film-forming polymer insoluble in the gastrointestinal tract fluids;

- ◆ 2C - at least one water-soluble polymer;
- ◆ 3C - at least one plasticizer;
- ◆ 4C - optionally at least one surfactant/lubricant preferably selected from the following group of products:
  - ~ anionic surfactants;
  - ~ and/or non-ionic surfactants,

■ and the liquid phase is saturated or becomes saturated with active principle(s) on contact with the microcapsules.

2. Suspension according to claim 1, characterized in that the families A, B and C from which the constituents of the coating composition are selected are as follows:

- ⇨ Family A
- ◆ 1A - ethyl cellulose and/or cellulose acetate;
- ◆ 2A - polyacrylamide and/or polyvinylpyrrolidone;
- ◆ 3A - castor oil;
- ◆ 4A - an alkali metal or alkaline earth metal salt of fatty acids, stearic and/or oleic acid being preferred, a polyethoxylated sorbitan ester, a polyethoxylated castor oil derivative, a stearate, preferably calcium, magnesium, aluminium or zinc stearate, a stearylfumarate, preferably sodium stearylfumarate, or glycerol behenate, taken individually or in a mixture with one another;
- ⇨ Family B
- ◆ 1B
  - ~ cellulose acetate-phthalate;
  - ~ hydroxypropyl methyl cellulose phthalate;
  - ~ hydroxypropyl methyl cellulose acetate-succinate;
  - ~ (meth)acrylic acid/(meth)acrylic acid alkyl (methyl) ester copolymer;
  - ~ and mixtures thereof;
- ◆ 2B
  - ~ hydrogenated vegetable waxes;
  - ~ triglycerides;
  - ~ animal and vegetable fats (beeswax, carnauba wax, etc.);
  - ~ and mixtures thereof.
- ⇨ Family C
- ◆ 1C
  - ~ water-insoluble cellulose derivatives, ethyl cellulose and/or cellulose acetate being particularly preferred;

- ~ acrylic derivatives;
- ~ polyvinyl acetates;
- ~ and mixtures thereof;
- ◆ 2C
- ~ water-soluble cellulose derivatives;
- ~ polyacrylamides;
- ~ poly-N-vinylamides;
- ~ poly-N-vinyllactams;
- ~ polyvinyl alcohols (PVA);
- ~ polyoxyethylenes (POE);
- ~ polyvinylpyrrolidones (PVP) (the latter being preferred);
- ~ and mixtures thereof;
- ◆ 3C
- ~ glycerol and its esters, preferably from the following subgroup: acetylated glycerides, glycerol monostearate, glyceryl triacetate and glycerol tributyrate;
- ~ phthalates, preferably from the following subgroup: dibutyl phthalate, diethyl phthalate, dimethyl phthalate and dioctyl phthalate;
- ~ citrates, preferably from the following subgroup: acetyltributyl citrate, acetyltriethyl citrate, tributyl citrate and triethyl citrate;
- ~ sebacates, preferably from the following subgroup: diethyl sebacate and dibutyl sebacate;
- ~ adipates;
- ~ azelates;
- ~ benzoates;
- ~ vegetable oils;
- ~ fumarates, preferably diethyl fumarate;
- ~ malates, preferably diethyl malate;
- ~ oxalates, preferably diethyl oxalate;
- ~ succinates, preferably dibutyl succinate;
- ~ butyrates;
- ~ cetyl alcohol esters;
- ~ salicylic acid;
- ~ triacetin;
- ~ malonates, preferably diethyl malonate;
- ~ cutin;
- ~ castor oil (this being particularly preferred);

- ~ and mixtures thereof;
- ◆ 4C
- ~ alkali metal or alkaline earth metal salts of fatty acids, stearic and/or oleic acid being preferred;
- ~ polyethoxylated oils, preferably polyethoxylated hydrogenated castor oil;
  polyoxyethylene/polyoxypropylene copolymers;
  polyethoxylated sorbitan esters;
  polyethoxylated castor oil derivatives;
  stearates, preferably calcium, magnesium, aluminium or zinc stearate;
  stearylfumarates, preferably sodium stearylfumarate;
  glycerol behenate;
  and mixtures thereof.

3. Suspension according to claim 1 or 2, characterized in that the film coating consists of a single layer.

4. Suspension according to claim 1, characterized in that it contains:
- 30 to 95% by weight and preferably 60 to 85% by weight of liquid phase (advantageously water);
- and 5 to 70% by weight and preferably 15 to 40% by weight of microcapsules.

5. Suspension according to claim 1, characterized in that the amount of solvent liquid phase (preferably water) for the active principle(s) is such that the proportion of dissolved active principle(s) originating from the microcapsules is less than or equal to 15% and preferably less than or equal to 5% by weight, based on the total weight of the active principle(s) contained in the microcapsules.

6. Suspension according to claim 1, characterized in that the liquid phase is at least partially and preferably totally saturated with active principle(s) following the incorporation of the microcapsules into this liquid phase.

7. Suspension according to claim 6, characterized in that it is the active principle(s) contained in the microcapsules that saturate the liquid phase.

8. Suspension according to claim 1, characterized in that the liquid phase is at least partially and preferably totally saturated with active principle(s) by means of non-encapsulated active principle(s) prior to the incorporation of the microcapsules into this liquid phase.

9. Suspension according to any one of claims 1 to 8, characterized in that the microcapsules have a particle size less than or equal to 1000 microns, preferably of between 200 and 800 microns and particularly preferably of between 200 and 600 microns.

10. Suspension according to any one of claims 1 to 9, characterized in that the film coating represents from 1 to 50% and preferably from 5 to 40% of the total weight of the coated microcapsules.

11. Suspension according to claim 10, characterized by an in vitro release profile obtained using a type II apparatus according to the European Pharmacopoeia 3rd edition, in a phosphate buffer medium of pH 6.8 and at a temperature of 37°C, such that:

- ► the proportion PI of active principle(s) released during the first 15 minutes of the dissolution test is such that:

$$PI \leq 15$$

preferably $PI \leq 5$;

- ► the remaining active principle(s) is (are) released over a period such that the release time of 50% by weight of AP ($t_{½}$) is defined as follows (in hours):

$$0.5 \leq t_{½} \leq 30$$

preferably $0.5 \leq t_{½} \leq 20$.

12. Suspension according to any one of claims 1 to 11, characterized in that:

- the initial in vitro release profile Pfi obtained just after suspension of the microcapsules in the solvent (preferably aqueous) phase, using a type II apparatus according to the European Pharmacopoeia 3rd edition, in a phosphate buffer medium of pH 6.8, at a temperature of 37°C,
- and the in vitro release profile Pf_{10} obtained 10 days after suspension of the microcapsules in the solvent (preferably aqueous) phase, using a type II apparatus according to the European Pharmacopoeia 3rd edition, in a phosphate buffer medium of pH 6.8, at a temperature of 37°C,

are similar.

13. Suspension according to any one of claims 1 to 12, characterized in that its pH is arbitrarily acidic or neutral.

14. Suspension according to any one of claims 1 to 13, characterized in that it comprises at least one rheology modifier.

15. Suspension according to any one of claims 1 to 14, characterized in that it comprises at least one agent for modifying the solubility of the active principle(s) in the solvent (preferably aqueous) liquid phase.

16. Suspension according to any one of claims 1 to 15, characterized in that it contains at least one additive selected from the group comprising surfactants, colourants, dispersants, preservatives, taste improvers, flavourings, sweeteners, antioxidants and mixtures thereof.

17. Suspension according to any one of claims 1 to 16, characterized in that the active principle(s) belongs (belong) to at least one of the following families of active substances: antiulcer drugs, antidiabetics, anticoagulants, antithrombics, hypolipidaemics, antiarrhythmics, vasodilators, antiangina drugs, antihypertensives, vasoprotectors, fertility promoters, labour inducers and inhibitors, contraceptives, antibiotics, antifungals, antivirals, anticancer drugs, anti-inflammatories, analgesics, antiepileptics, antiparkinsonism drugs, neuroleptics, hypnotics, anxiolytics, psychostimulants, antimigraine drugs, antidepressants, antitussives, antihistamines and antiallergics.

18. Suspension according to claim 17, characterized in that the AP is selected from the following compounds: pentoxifylline, prazosin, aciclovir, nifedipine, diltiazem, naproxen, ibuprofen, flurbiprofen, ketoprofen, fenoprofen, indomethacin, diclofenac, fentiazac, oestradiol valerate, metoprolol, sulpiride, captopril, cimetidine, zidovudine, nicardipine, terfenadine, atenolol, salbutamol, carbamazepine, ranitidine, enalapril, simvastatin, fluoxetine, alprazolam, famotidine, ganciclovir, famciclovir, spironolactone, 5-asa, quinidine, perindopril, morphine, pentazocine, metformin, paracetamol, omeprazole, metoclopramide, atenolol, salbutamol morphine, verapamil, erythromycin, caffeine, furosemide, cephalosporins, montelukast, valaciclovir, ascorbic acid salts, diazepam, theophylline, ciprofloxacin, vancomycin, aminoglycosides, penicillins (except for amoxicillin) and mixtures thereof.

19. Drug, characterized in that it comprises a suspension according to any one of claims 1 to 18.

20. Drug, characterized in that it comprises a kit for preparing the suspension according to any one of claims 1 to 18, said kit containing:

- microcapsules in substantially dry form containing the active principle(s) for saturating the liquid phase with active principle(s) once the two solid and liquid phases have been brought into contact;
- and/or a mixture of microcapsules in substantially dry form containing the active principle(s) in the dose that is just necessary for modified release, together with immediate-release uncoated active principle(s) in a necessary and sufficient dose to saturate the liquid phase with active principle(s) once the saturation dose of active principle(s) and the liquid phase have been brought into contact;
- and the liquid phase and/or at least part of the ingredients useful for its preparation, and/or the protocol for preparation of the suspension.

Key to Figures

Fig. 1:
dissous = dissolved
profil initial = initial profile
profil après 10 jours = profile after 10 days
heures = hours

Fig. 2:
Profil initial = Initial profile
Profil après 19 jours = Profile after 19 days

Fig. 3:
dissous Metformine = metformin dissolved
Profil initial = Initial profile
Profil après 12 jours = Profile after 12 days
Temps (en heures) = Time (in hours)